REMARKS

Claims 72-82 and 85-88 are pending in this application. Applicants thank the Examiner for the withdrawal of several objections and rejections in previous Office Actions.

Claims 85-88 are newly added in this response. Support for new claim 85 can be found at, *inter alia*, page 6, lines 4-5 (characterization of antibodies); page 12, lines 14-18 and lines 23-34 (providing cells expressing TMPRSS2); page 32, lines 7-11 (ATCC deposit 207097); page 14, lines 15-16 (providing an antibody that binds TMPRSS2); page 32, lines 24-34 (administering antibody to cancer cells); and page 19, lines 19-36 (evaluating the antibody). Support for new claim 86 is found at, *inter alia*, page 19, lines 29-34 (identifying the mechanism of the antibody). Support for new claims 87 and 88 is found at, *inter alia*, page 19, lines 19-34 (in vitro assays to inhibit growth of tumor cells, and identifying the mechanism thereof).

A replacement Figure 3 has been submitted to highlight all amino acid differences in bold type. This obviates the objection raised to Figure 3 in the Office Action mailed July 3, 2000, Paper No. 10, on page 4, first paragraph.

Draftsperson's objections

The Draftsperson raised objections to several figures in the Notice of Draftperson's Paetnt Drawing Review attached to Paper No. 10.

Figure 1 was objected to for improper margins. The margins have been corrected to conform to 37 C.F.R. 1.84(g). Figure 1 was also objected to for "Views not labeled separately or properly." However, there is only one view in Figure 1, which cannot be labeled separately; accordingly, Applicants traverse this objection.

Figure 2 has been amended to separately label the two sequences presented therein.

Figure 3 has been amended to increase the character size as required, in addition to the amendment required by the Examiner addressed above.

Figures 4-9 have been amended as required by the Draftsperson.

The drawings as amended should address all objections by the Draftsperson.

Interview with Examiner

The Applicants express their gratitude for the interview with Examiner Nickol of September 9, 2003, and the interview with Examiners Anthony Caputa and Examiner Nickol on October 6, 2003. The time and consideration of the Examiners is greatly appreciated.

The substance of the interviews is hereby made of record as directed by MPEP § 713.04. The interview of September 9, 2003 took place between Examiner Nickol, Timothy Lithgow of the assignee (Agensys), and the undersigned agent. No exhibits were shown nor any demonstrations presented. Claims 72-82 were discussed. No specific prior art was discussed; the art cited in Paper Nos. 34 and 37 was discussed in a general sense. Claims directed to *in vitro* embodiments of the invention were discussed; such claims are presented here as claims 87-88. The general thrust of the principal arguments focused on the enablement rejection; in particular, clarification of what specific aspect of the claims was not enabled was sought, and arguments were presented that each element of the claim is fully enabled. Agreement was not reached.

The interview of October 6, 2003 took place between Examiner Nickol, Supervisory Primary Examiner Anthony Caputa, Timothy Lithgow of the assignee (Agensys), and the undersigned agent. A draft of the Declaration of Arthur B. Raitano, Ph.D. (which is presented here) was sent to the Examiners for review. No demonstrations were presented. Claims 72-82 and the claims newly presented here as claims 85-88 were discussed. The general thrust of the principal arguments again focused on the enablement rejection; again, clarification was sought as to what aspects of the claims were not enabled. Agreement was not reached.

Information Disclosure Statement

An Information Disclosure Statement was filed on October 23, 2002 in this application. However, the completed and initialed form PTO-1449 was not returned with the current Office Action. Applicants would appreciate the Examiner's consideration of the references disclosed in that Information Disclosure Statement, and initialing and return of the form PTO-1449 to the Applicants. If the Information Disclosure Statement has not been matched to the file, upon the request of the Examiner, the Applicants can supply a copy of the Information Disclosure Statement and references thereof, as well as proof of receipt by the United States Patent and Trademark Office of the original IDS filing.

New Rejection under 35 U.S.C. § 112, first paragraph, written description

Claims 72-82 were rejected as failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph, as there was insufficient assurance that the deposit referenced at page 32, lines 9-11 of the specification was made under the conditions specified in 37 C.F.R. § 1.801-1.809.

Applicants hereby state that 1) all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on the application, and 2) that the deposit will be replaced if viable samples cannot be dispensed. Applicants reserve the right to request notice by the depository to the depositor of the name and address of the party to whom a deposit is furnished, as permitted by 37 C.F.R. § 1.808(a)(2) and 37 C.F.R. § 1.808(b).

Maintained Rejection under 35 U.S.C. § 112, first paragraph, enablement

Claims 72-82 were rejected as failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, for various reasons. This rejection was discussed during the interview of September 9, 2003 and the interview of October 6, 2003. Again, the Examiners' time and effort is greatly appreciated.

The Applicants again traverse this rejection, and submit the Declarations of Arthur B. Raitano, Ph.D. and Mary Faris, Ph.D. in support of this traversal.

The Examiner appears to be examining the claims as "method of treatment" claims, as indicated in Paper No. 34 in the paragraph bridging pages 7 and 8. However, the claim does not read "A method of treatment, comprising..." but rather reads as "A method for inhibiting the growth, viability and/or survivability of cancer cells..." It is well established that a limitation cannot be imported into the claims from the specification (*In re Prater*, 415 F.2d 1393, 1404 (CCPA, 1969)). As Dr. Raitano notes in his Declaration, the method of claim 72 (and claims 73-78 as well) can be used for purposes other than treatment, such as characterization of a cancer cell (Raitano Declaration, paragraph 12) and antibody screening (Raitano Declaration, paragraph 9). Indeed, new claims 85-88, which are directed to methods of characterization of an antibody and *in vitro* inhibition of cell growth, are directed to such non-treatment applications. And while claims 79-82 are directed to a method of administering the antibodies when the cancer cells are in a mammal, even these claims read on purposes other than treatment, such as diagnostic

methods. Applicants therefore submit that the claims should be examined as written. When this is done, it is seen that the claims are fully enabled. This conclusion is supported by the Raitano Declaration.

Even for an application such as treatment, Applicants submit that the claim is enabled. The application teaches how to make and use the claimed invention in such clear terms as to enable those skilled in the art to practice the invention. Dr. Arthur Raitano's Declaration addresses this at length. The enablement of the claim as written is discussed element-by-element below.

The specification teaches the sequence of the 20P1F12/TMPRSS2 protein (at, *inter alia*, Figure 3). The specification, and the knowledge of those of skill in the art, both teach how to raise antibodies against this protein (at, *inter alia*, page 15, line 25 to page 17, line 22), and the specification indicates the successful generation of antibodies that bind specifically to 20P1F12/TMPRSS2 at page 33, lines 1-14. The procedure for raising antibodies to the desired antigen is specifically addressed by Dr. Arthur Raitano in paragraph 7 of his Declaration.

One example of a protocol for intravenous administration of the antibodies, including formulations and dose ranges, is given at page 21, lines 12-28 of the specification. Dr. Arthur Raitano addresses this in paragraph 8 of his Declaration, where he discusses how the antibodies can be administered.

Regarding the use recited in the preamble, "[a] method for inhibiting the growth, viability, and/or survivability of cancer cells...," the specification, and the knowledge of those of skill in the art, teach how to use the antibodies for inhibiting the growth, viability and/or survivability of cancer cells (see, *inter alia*, page 17, line 24 to page 21, line 35). The Raitano Declaration, in paragraph 11, discusses the "scientifically reasonable expectation that engagement of a protein with an antibody specific for that protein" will elicit a consequence that would inhibit the growth, viability and/or survivability of a cancer cell expressing 20P1F12/TMPRSS2. Thus, those of skill in the art can generate antibodies against 20P1F12/TMPRSS2 and administer those antibodies to cancer cells expressing 20P1F12/TMPRSS2, with a reasonable expectation that this will inhibit the growth, viability and/or survivability of the cancer cells.

Dr. Raitano's expert testimony has not yet been addressed in writing, and there is no evidence of record in the application that could rebut the evidence provided in this Declaration.

The Applicants respectfully request consideration of the Raitano Declaration in support of their arguments.[1]

In view of the extensive teachings in the specification, as well as the knowledge of those of skill in the art, as to how to make and use the invention, it is respectfully submitted that the invention is fully enabled. It appears that the rejection boils down to a question of whether the invention actually works as intended, which is a question to be resolved under the law pertaining to 35 U.S.C. § 101, and which is discussed below.

The Examiner stated that data on the efficacy of antibody treatment in animals was required because the method claims could read on a method of treating cancer. See Paper No. 38, the Examiner's Interview Summary for the interview of September 9, 2003, where the Examiner indicates that "Applicants were informed that experimental data was necessary to overcome the 112, 1st paragraph rejection." (emphasis original). The Applicants respectfully disagree with this requirement.

There is no basis in statutory law or regulation for this requirement. In the interviews of September 9, 2003 and October 6, 2003, the Examiner indicated that the rejection was based on the Wands factors (*In re Wands,* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). However, the rejection in Paper No. 37 is not framed in terms of the Wands factors, making it difficult to determine exactly which Wands factor(s) the rejection is based upon, and how to respond to the rejection. It should also be noted that *In re Wands* does not contain a *per se* rule for experimental data. The rejection in Paper No. 34 (which is maintained in Paper No. 37) cites two of the Wands factors, the presence or absence of working examples in the specification and the predictability of the art. However, other Wands factors, such as the amount of experimentation necessary to make and use the invention based on the contents of the disclosure, and the level of ordinary skill in the art, are not taken into account, despite Patent and Trademark Office policy that it is "improper to conclude that a disclosure is not enabling based on an

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[1] This request is respectfully made in light of the policy for treatment of expert declarations described in MPEP 706.01(B): "Evidence traversing rejections must be considered by the examiner whenever present. All entered affidavits, declarations, and other evidence traversing rejections are acknowledged and commented upon by the examiner in the next succeeding action. ... Where the evidence is insufficient to overcome the rejection, the examiner must specifically explain why the evidence is insufficient. General statements such as "the declaration lacks technical validity" or "the evidence is not commensurate with the scope of the claims" without an explanation supporting such findings are insufficient."

analysis of only one of the above factors while ignoring one or more of the others" (MPEP § 2164.01(a)). The Declaration of Dr. Raitano addresses the enablement issue at length.

Turning to the argument made by the Examiner in Paper No. 37, in the paragraph bridging pages 2 and 3, the Examiner notes that the Applicants have pointed out that U.S. 5,770,195 did not teach the expression of Her2/neu on cardiac tissue, and states that "this argument has been considered but is not found persuasive, as Applicants have stated for the record that the HER-2 receptor is indeed expressed on cardiac tissue." This is exactly the point: the Applicants are arguing that Her2/neu is expressed on normal cardiac tissue, and yet this has not affected the clinical or commercial success of the Her2/neu antibody.

The Examiner then raises the issue that the 20P1F12/TMPRSS2 antigen is present in normal tissue as well. Applicants respectfully request that the Examiner consider the Declaration of Mary Faris, Ph.D., regarding the utility of antibody therapy where the corresponding antigen is located on both normal and malignant tissue. Specifically, paragraphs 7, 8, and 9 of the Faris Declaration expressly consider normal tissue expression of Her2/neu antigen and the efficacy of the anti-Her2/neu antibody Herceptin®; paragraphs 11-15 of the Faris Declaration expressly consider normal tissue expression of epidermal growth factor receptor (EGFR) and the efficacy of Erbitux™, an antibody against EGFR.

It should be noted again that these concerns should be addressed in a utility rejection; the Examiner is contending that the invention will not work. However, the Herceptin® antibody and the Erbitux™ antibody are usable and useful treatments despite the presence of appreciable levels of antigen on normal tissue as well as on malignant tissue, which rebuts any assertion that there is a lack of utility due to normal tissue expression. Indeed, the Her2/neu antigen is present on vital tissues such as heart and kidney, and the EGFR receptor is present in several tissues, including tissues from vital organs such as brain and colon. Rejection on the basis of normal tissue expression is therefore inappropriate under either 35 U.S.C. § 112, first paragraph, or under 35 U.S.C. § 101, and withdrawal of the rejection is respectfully requested.

The Examiner's rejection on the basis of antigenic heterogenicity (reiterated from the Office Action mailed August 23, 2003, Paper No. 34) is also respectfully traversed. The Examiner had stated in that previous Office Action that "one of the major obstacles to successful monoclonal antibody therapy is antigenic heterogenicity and insufficient target

specificity...heterogenicity of antigen expression by tumor cells restricts the percentages of cells that can be reliably targeted. ... Thus, one of skill in the art, upon reading the disclosure, would not reasonably predict that the claimed method would selectively and specifically inhibit the growth of cancer cells expressing 20P1F12/TMPRSS2 as there is insufficient guidance and objective evidence that 20P1F12/TMPRSS2 is overexpressed in cancer cells versus normal cells." (Paper No. 34, page 9; citations omitted.)

The Examiner's attention is drawn to page 5, lines 29-30 of the instant specification where it is disclosed that expression in kidney, pancreas and lung tissue is 10- to 20-fold lower than expression in prostate. If the Examiner is contending that cancer cells express antigens at varying levels, it should be noted from Figure 7 in the specification that a variety of cancer cell lines strongly express the 20P1F12/TMPRSS2 protein. As the Faris Declaration (paragraph 16) points out, expression of antigens on normal cells as well as malignant cells does not necessarily destroy the efficacy of a monoclonal antibody therapeutic. And as the Raitano Declaration (paragraph 11) points out, it is scientifically reasonable that the anti-TMPRSS2 protein will inhibit the growth, viability, and/or survivability of the cancer cells expressing TMPRSS2.

If the Examiner is arguing that expression of the antigen on normal prostate tissue as well as cancerous prostate tissue may cause complications in treatment of prostate cancer, it should be noted that surgical treatment of prostate cancer also affects normal prostate tissue, since the entire prostate—healthy portions as well as diseased portions—is often removed in surgery. Even if the anti-TMPRSS2 antibody completely obliterates the prostate, this is no more than what typically happens during radical prostatectomy, and the antibody-mediated therapy avoids surgical trauma and complications.

Once again, these concerns should be addressed via a utility rejection; the rejection expresses doubt that the invention will work for the intended purpose, and does not address whether those of skill in the art can practice the invention from the teachings in the specification. Thus, Applicants respectfully request that any rejections based on normal tissue expression or antigenic heterogenicity should be withdrawn.

Finally, the Examiner states that "there is no evidence to support that any antibody therapy would predictably target and successfully destroy the prostate gland..." This issue is addressed by the Raitano Declaration (see paragraphs 9 and 11). However, this rejection is inconsistent with the Examiner's argument immediately above; the "antigenic heterogenicity"

rejection argues against the patentability of the claims because the antibody may adversely affect normal tissue, while this rejection denies patentability because the antibody may not adversely affect all malignant and normal tissue. Both arguments cannot be used, as the logic of one argument undercuts the logic of the other argument.

Again, these concerns are more properly framed as a utility rejection, not an enablement rejection—the Examiner is implicitly asking the question, "Will the invention work?" In regards to this point, it should be noted that many therapies are often used which do not completely destroy malignant tissue; radiation therapy and chemotherapy may not completely destroy all cancerous tissue or even an entire diseased organ, but they are employed to delay the complications of the disease or to alleviate symptoms of the disease. The evidence discussed herein supports the contention that antibody-based compositions can inhibit the growth of malignant tissues. As one example, paragraph 11 of the Faris Declaration describes the effects that Erbitux™ has on tumor size and the beneficial effects for the patient, even though the tumor is not completely destroyed.

In light of the foregoing, withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested. And even should the rejections be made under 35 U.S.C. § 101, Applicants have demonstrated a specific, substantial, and credible use for the invention, which obviates any possible rejection on the basis of utility. Allowance of the pending claims in view of the evidence and arguments presented herein is respectfully requested.

CONCLUSION

Applicants submit that all outstanding objections and rejections have been addressed by this response. A Notice of Allowance is earnestly and respectfully solicited. The Examiner is invited to call the undersigned agent if the Examiner believes that any issues can be resolved via a telephone conference.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 511582000800.

Respectfully submitted,

Dated: November 20, 2003 By: _____

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Enclosures: Declaration of Arthur B. Raitano, Ph.D. under 37 C.F.R. § 1.132, with Exhibit A
Declaration of Mary Faris, PH.D. Concerning Normal Tissue Expression, with Exhibits A-V
replacement Figure 1
replacement Figure 2
replacement Figure 3
replacement Figure 4
replacement Figure 5
replacement Figure 6
replacement Figure 7
replacement Figure 8
replacement Figure 9